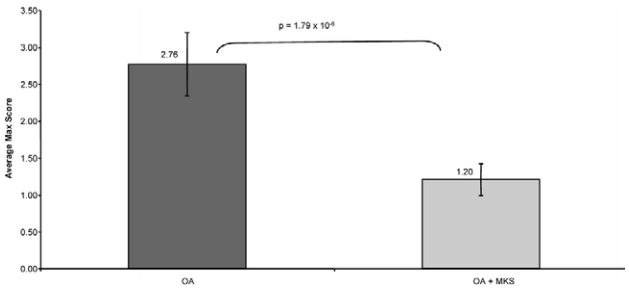

Figure 1. Effect of Montelukast treatment on Mean Maximal Knee OA Score (± SEM).

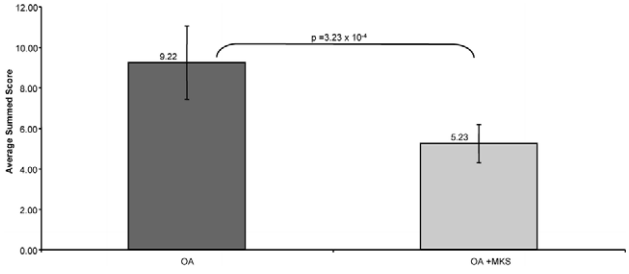

Figure 2. Effect of Montelukast treatment on Mean Summed Knee OA Score (± SEM).

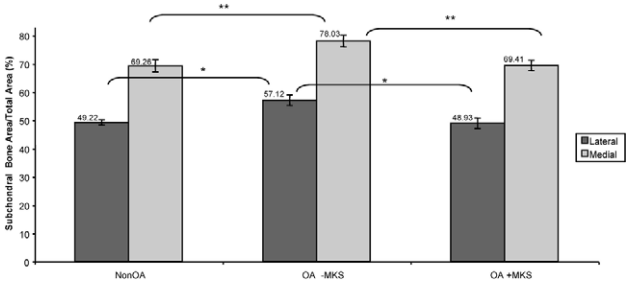

Figure 3. Reversal of sclerotic changes in subchondral bone with Montelukast (MKS) treatment. *p-value <0.005, **p-value <0.05.

indirect effect of decreased cartilage damage on aberrant bone remodeling.

Conclusions: The dual goals of translation research are to discover novel disease mechanisms and to transform this information into new therapeutics for human disorders. Here we present data that implicate cysteinyl leukotrienes in early OA progression. Therefore, targeting of this pathway could represent an important area to OA research and treatment. In addition, the apparent similarities of the DMM model to humans at risk for OA from meniscal damage, suggests that treatment proximal to the time of meniscal repair with CysLT antagonists could delay the structural progression of incipient OA. Subchondral bony sclerosis is a contributing co-factor in OA progression. Although, the reduction in cartilage damage observed in this study could be seen as the most clinically relevant outcome for montelukast treatment of OA, prevention of abnormal bone remodeling could have equally important outcomes in OA joint prophylaxis.

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DISEASE MODIFYING EFFECTS OF A CATHEPSIN K INHIBITOR IN THE RABBIT ANTERIOR CRUCIATE LIGAMENT TRANSECTION MODEL OF OSTEOARTHRITIS

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Purpose: There is increasing evidence that subchondral bone remodeling may contribute to the pathogenesis of OA, in both disease initiation and progression. In this study, we investigated the potential role of cathepsin K (CatK) as a disease-modifying target in the rabbit anterior cruciate ligament transection (ACLT) model of osteoarthritis. To test the hypothesis, we evaluated the disease modifying effects of two different bone resorption inhibitors, L-006235, a potent inhibitor of Cat K, and compared to the bisphosphonate Alendronate (ALN), on subchondral bone integrity, cartilage degradation, and osteophyte formation in the rabbit ACLT model.

Methods: Male NZW rabbits (N= 35) underwent anterior cruciate ligament transection (ACLT) or sham-operation in the right knee. The animals were dosed at one-week post-surgery with either the CatK inhibitor L-235 (10 or 50mg/kg, p.o., daily) or ALN (0.6mg/kg/wk, s.c.) for 8 weeks treatment duration. Rabbits were randomized and assigned into 5 groups: Sham + vehicle (V); ACLT + V; ACLT + ALN; ACLT + 10mg/kg L-235; ACLT + 50mg/kg L-235. Disease progression was evaluated by modified Mankin score. Subchondral bone volume and osteophyte area were measured by histomorphometric analysis. Urine levels of helical peptide, a marker for bone resorption and CTX-II, a cartilage degradation marker were measured at 3, 5, and 7 wk-post-surgery. Immunostaining of CatK and TRAP staining was performed to identify cells expressing CatK protein and osteoclasts, respectively.

Results: In the ACLT-rabbits, CatK is highly expressed in osteoclasts localized to the subchondral bone region of the affected joints. CatK expression is also found to be elevated in synovial fibroblasts, macrophages, and cells in the superficial region of articular cartilage. In addition to mediating bone matrix degradation, detection of high CatK expression in other cell types suggests that it may also be directly responsible for cartilage ECM degradation. Moreover, subchondral bone resorption in the tibial plateau was significantly increased in the ACLT-joints at 5-wk post-surgery. Treatment with either dose of L-235 or with ALN for 8-weeks effectively suppressed subchondral bone loss in the ACLT-joints. Furthermore, L-235 dose-dependently reduced osteophyte incidence and area. The CatK inhibitor and ALN were partially chondroprotective as determined by histological evaluation and type II collagen degradation marker. L-235 at 10mg/kg, were previously demonstrated to fully protect estrogen-deficiency induced bone loss in rabbits. While this dose of L-235 provided no chondroprotective effects as determined by Mankin score, 50mg/kg L-235 and ALN provided 48% ($p<0.001$) and 46% ($p<0.001$) chondroprotection, respectively. L-235 and ALN both inhibited osteophyte formation by 56% ($p<0.001$) and 38% ($p<0.001$), respectively. TRAP staining multinuclear cells were positive for CatK immunostaining, and these cells were observed in subchondral region of ACLT joint. Interestingly, in L-235-treated joint, TRAP(+) cells were small and number of nuclei was low.

Conclusions: Taken together, the data from this study support the important role of subchondral bone remodeling in the pathogenesis of OA in preclinical models. Furthermore, an oral, potent and selective CatK inhibitor may present an effective disease modifying therapy for the treatment of osteoarthritis.